REMARKS

Entry of the Amendment and reconsideration of the claims in view of the following Remarks is requested.

Claims 47, 54, and 59 are amended. The support for the amendments can be found throughout the specification, including at page 104, line 22 to page 106, line 23 (Example 4.C.); and page 106, line 25 to page 107, line 22.

Double Patenting

Claims 47-63 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 88-109 of copending Application No. 09/863,693. Claims 47-63 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 30-43, 45-51 and 53-55 of copending Application No. 09/373,403. Claims 47-63 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 45-82 of copending Application No. 10/143,437. Applicants request these rejections be held in abeyance until notice of allowable subject matter.

35 U.S.C. § 112, first paragraph

Claims 47-52 were rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement. While not acquiescing to the rejection and solely to expedite prosecution, claim 47 no longer refer to a first and second variable light chain domain rendering the rejection moot.

Applicants traverse this rejection.

35 U.S.C. 102(b)

Claims 47, 52-54 and 58 were rejected under 35 U.S.C. 102(b) as being anticipated by Nissim (Nissim, A. et al., the EMBO Journal 13(3), 1994), and as evidenced by Merchant (Merchant, A.M. et al., Nature Biotechnology,16, 1998). Applicants respectfully traverse this rejection.

Under 35 U.S.C. §102, "A claim is anticipated only if each and every element as set forth

in the claim is found either expressly or inherently described in a single prior art references." Verdegaal Bros. v. Union Oil of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The fact that a *certain* result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. MPEP § 2112. The prior art characteristic must be established as a certainty, probabilities are not sufficient. In re Oelrich, 666 F.2d 578, 581 (CCPA 1981).

Applicants' claim 47 is directed to a bispecific antibody comprising a first polypeptide and a second polypeptide, wherein: (a) the first polypeptide comprises a first heavy chain variable domain, a light chain variable domain and wherein a first binding domain is formed by the first heavy chain variable domain and the light chain variable domain; (b) the second polypeptide comprises a second heavy chain variable domain, the light chain variable domain, wherein a second binding domain is formed by the second heavy chain variable domain and the light chain variable domain, and wherein the first and second binding domains bind different antigens; and (c) the first and second polypeptides dimerize to form a bispecific antibody.

Applicants' claim 54 is directed to a bispecific antibody comprising a first polypeptide and a second polypeptide, wherein: (a) the first polypeptide comprises a first heavy chain variable domain, a first multimerization domain, a light chain variable domain, and wherein a first binding domain is formed by the first heavy chain variable domain and said light chain variable domain; (b) the second polypeptide comprises a second heavy chain variable domain, a second multimerization domain, said light chain variable domain, wherein a second binding domain is formed by the second heavy chain variable domain and said light chain variable domain, and wherein the first and second binding domains bind different antigens; and (c) the first and second polypeptides dimerize by interaction of the first and second multimerization domain to form a bispecific antibody, wherein the first and second multimerization domains each comprise a C_H3 region of an antibody constant domain.

Applicants submit Nissim et al. does not teach all of the elements of Applicants' claims. Applicants submit that Nissim et al. is directed to the development of a library of V_H scFv with randomized CDRH3 regions for isolating an antibody or fragment thereof that binds to a single antigen. The phage library is screened against single antigens separately and there is no teaching or suggestion in this reference that a multispecific antibody comprising at least two

binding domains that bind to different antigens can or should be made using the process as described in Nissim et al. In contrast, the claims provide for a bispecific antibody that comprises two binding domains that bind to different antigens.

There is no teaching or suggestion in the Nissim reference that bispecific antibodies can or should be formed wherein each binding domain binds to a different antigen and has the same light chain. The Nissim et al. reference does not teach or even suggest heteromultimeric bispecific antibodies having common light chains as well as multimerization domains that interact with one another to increase specific heterodimeric association of the polypeptides and avoid mispairing. As provided in Applicants' originally filed specification, the multimerization domain promotes interaction between a specific first polypeptide and a specific second polypeptide, thereby enhancing the formation of the desired heteromultimer and substantially reducing the probability of the formation of undesired heteromultimers or homomultimers (see page 19, line 15 to page 21, line 2, and particularly page 19, lines 19-24 of the specification).

With respect to the examiner's comments regarding " multimers" in Nissim et al., Applicants submit these comments miss the significance of Applicant's invention and it's difference from anything that is disclosed in Nissim et al. The "multimers" in Nissim et al. were actually aggregates formed randomly by such conditions as concentration during purification, or acid elution and neutralization during purification of single chain Fv polypeptides that have single antigen specificity (see Nissim et al., page 695, column 2, second full paragraph to page 696, column 1). In addition, on page 696, col. 1, Nissim et al. disclose that it is desirable to drive the self-aggregation of scFv fragments. Such self-aggregation teaches monospecificity of an aggregate and random association of the monomers and thus, teaches away from Applicants' invention of a method of preparing multichain, bispecific antibodies wherein the different polypeptides of the bispecific antibody associate with one another by specific interactions of the multimerization domains, and wherein the polypeptides form different antigen binding domains with the same light chain. There is no showing in Nissim et al. those multimerization domains which interact with one another to form heteromultimeric bispecific antibodies as claimed by Applicants are formed in the random, self-aggregates of Nissim et al. Thus, Nissim et al. does not teach or suggest Applicants' claimed invention.

Applicants submit that, at least for these reasons, the Nissim et al. reference does not

disclose all of the elements of Applicants' claims and, therefore, does not anticipate the claims. Applicants request withdrawal of the rejection.

Claims 59, 60 and 63 were rejected under 35 U.S.C. 102(b) as being anticipated by Hu (Hu, S. et al., Cancer Res. 56, 1996)) because the claims fail to recite that each of the binding domains binds to different antigens. While not acquiescing to the rejection and solely to expedite prosecution, claim 59 now indicates that each binding domain of the bispecific antibody binds to different antigens. Withdrawal of the rejection is requested.

Claims 47, 48, 50, 52-54, 56 and 58 were rejected under 35 U.S.C. 102(b) as being anticipated by de Kruif (de Kruif et al., The Journal of Biological Chemistry, 271(13), March 1996) and as evidenced by Merchant (supra). Applicants respectfully traverse.

Applicants' claim 47 is directed to a bispecific antibody comprising a first polypeptide and a second polypeptide, wherein: (a) the first polypeptide comprises a first heavy chain variable domain and a light chain variable domain and wherein a first binding domain is formed by the first heavy chain variable domain and the light chain variable domain; (b) the second polypeptide comprises a second heavy chain variable domain and the light chain variable domain, wherein a second binding domain is formed by the second heavy chain variable domain and the light chain variable domain, and wherein the first and second binding domains bind different antigens; and (c) the first and second polypeptides dimerize to form a bispecific antibody.

Applicants' claim 54 is directed to a bispecific antibody comprising a first polypeptide and a second polypeptide, wherein: (a) the first polypeptide comprises a first heavy chain variable domain, a first multimerization domain and a light chain variable domain, and wherein a first binding domain is formed by the first heavy chain variable domain and said light chain variable domain; (b) the second polypeptide comprises a second heavy chain variable domain, a second multimerization domain and said light chain variable domain, wherein a second binding domain is formed by the second heavy chain variable domain and said light chain variable domain, and wherein the first and second binding domains bind different antigens; and (c) the first and second polypeptides dimerize by interaction of the first and second multimerization domain to form a bispecific antibody, wherein the first and second multimerization domains each comprise a C_H3 region of an antibody constant domain.

The de Kruif et al. reference cited by the Examiner does not describe or discuss the light chain sequence of the scFvs. Moreover, the only bispecific molecule made in de Kruif et al. has different light chains. Clone 3F(IgG2) and clone 23J (DNP5) were used to make a bispecific antibody. As shown in the de Kruif, JMB 248:97 (1995), the scFv to IgG2 has a light chain encoded by members of theV_k1 gene family and ScFv to DNP5 has a light chain encoded by members of the V_λ 3 gene family (See de Kruif, JMB, (1995) page 98, col. 2, and Table 3. There is no teaching or suggestion that the light chains are the same or that the bispecific molecule can or should be formed having the same light chain.

Nissim et al. discloses a library of scFvs, but is silent on the sequence of the variable light chain domain. There is no teaching or suggestion in the Nissim et al. reference or the de Kruif et al reference that bispecific antibodies can or should be formed wherein each binding domain binds to a different antigen and has the same light chain.

With respect to claim 54, Applicants further submit that the de Kruif et al reference does not teach or suggest a bispecific antibody that has a first and second multimerization domains each comprising a C_H3 region of an antibody constant domain. The scFv constructs of de Kruif et al do not have any C_H3 region sequences.

Applicants submit that, at least for these reasons, the de Kruif et al. reference does not disclose all of the elements of Applicants' claims and, therefore, does not anticipate the claims. Applicants request withdrawal of the rejection.

35 U.S.C. 103(a)

In order to establish a prima facie case of obviousness, three basic criteria must be met, namely: 1) the references when combined must teach or suggest all of the claim limitations; 2) there must be suggestion or motivation to modify the reference or combine the reference teachings, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art; and 3) a reasonable expectation of success. MPEP 706.02(j). Applicants submit that not all of these requirements have been met, in the least, because the references even when combined do not teach all the limitations of the claims, and there is no motivation to combine the references in the manner suggested by the Examiner.

Claims 47-49, 52-55, 58-61 and 63 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over de Kruif (de Kruif et al., JBC 271(13):7630-7634 (1996)) as evidenced by Merchant et al. (Merchant et al., Nature Biotechnology 16:677-681 (1998)) in view of Ridgway (Ridgway et al., Protein Eng. 9:617-621 (1996)). Applicants respectfully traverse.

Applicants claim a bispecific antibody formed by dimerization of first and second polypeptides comprising first and second binding domains formed by the same light chain variable domain and first or second heavy chain variable domains.

de Kruif et al. disclose a bispecific scFv molecule in which the light chains are different (as pointed out hereinabove).

Merchant et al. refers to Nissim et al., EMBO J.13:692-698 (1994). Nissim et al. does disclose a library of scFvs but does not disclose or even suggest that common light chains for the individual scFvs. Further, Nissim et al. does not disclose or even suggest bispecific antibodies having common light chains.

Ridgeway, et al. (Protcin Eng. 9:617-621 (1996)) discloses antibodies having antibody constant regions engineered to produce complementary protuberances and cavities. Ridgway does not disclose or suggest bispecific antibodies having common light chains.

Applicants submit that even when all of the references are combined, they do not disclose all of the elements of the claimed invention. None of the cited references disclose or suggest bispecific antibodies having common light chains. Combining references that disclose scFv libraries lacking bispecific antibodies having common light chains (de Kruif et al. and Nissim et al.) with a reference that discloses engineered CH3 multimerization domains, still fails to yield Applicants' invention. As a result, the references cannot properly be combined and the examiner has not met the burden of showing prima facie obviousness of Applicants' invention with respect to the cited references.

In addition, there is no motivation for one of ordinary skill in the art to combine references each of which lacks the same feature of Applicants' invention – a bispecific antibody having a common light chain. One of ordinary skill in the art would not be motivated to combine references to provide a feature not disclosed or suggested by any of the references. As a result, the references cannot properly be combined and the examiner has not met the burden of showing prima facie obviousness of Applicants' invention with respect to the cited references.

Withdrawal of the rejection is respectfully requested.

Claims 47-63 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over de Kruif (de Kruif et al., JBC 271(13):7630-7634 (1996)) as evidenced by Merchant (Merchant et al., Nature Biotechnology 16:677-681 (1998)) in view of Ridgeway (Ridgway et al., Protein Eng. 9:617-621 (1996)) and further in view of Hu (Hu et al., Cancer Research 56:3055-3061 (1996)). Applicants respectfully traverse.

Applicants submit that even when all of the references are combined, they do not disclose all of the elements of the claimed invention. As stated above, the present claims provide for a bispecific antibody comprising the same light chain variable domain including a common variable light chain domain that has at least 98% sequence identity to each variable light chain domain of a first and second antibody, wherein the first and second antibody bind to different antigens. Applicants have discovered and disclosed that common light chain variable domains can likely be found for any V_L comparison of antibodies directed against different antigens (Example 4). The claimed bispecific antibody having a common light chain variable domain is useful in that it reduces the mispairing of light and heavy chains.

As discussed above, none of the cited references alone or in combination teach all of the elements of the claims. The de Kruif et al. reference cited by the examiner does not describe or discuss the light chain sequence of the scFvs in the library described in the paper. Moreover, as discussed previously, the only bispecific molecule made has different light chains. There is no teaching or suggestion that the bispecific molecule can or should be formed having the same light chain.

With respect to claim 54, Applicants further submit that the de Kruif et al reference does not teach or suggest a bispecific antibody that has a first and second multimerization domain each comprising a C_H3 region of an antibody constant domain. The scFv constructs of de Kruif et al do not have any C_H3 region sequences.

Hu et al discusses the presence of a CH3 domain to provide for homodimers of a scFv specific for a single antigen. There is no discussion in Hu et al of bispecific antibodies or that such bispecific antibodies should have common light chains. Ridgway et al. also does not teach or suggest that a bispecific antibody should have the same or a common light chain in both binding domains.

While Applicants contend that even combined the cited references do not disclose all of the elements of the claims, Applicants also contend there is no motivation to combine these references. "A rejection cannot be predicated on the mere identification . . . of individual components of the claimed invention." Rather, particular findings must be made as to the reason the skilled artisan, with no known knowledge of the claimed invention, would have selected these components for combination in the manner claimed." *Ecolochem Inc. v. Southern Calif. Edison Co.*, 227 F3d 1361, 1375 (Fed. Cir. 2000). Applicants submit the Examiner is using hindsight reconstruction to piece together pieces of individual references to reject the claims as obvious.

None of the cited references, alone or in combination, teach the desirability of, or advantage to, having a common light chain variable domain for a bispecific antibody over other light chains, or a common variable light chain variable domain having at least 98% sequence identity to each variable light chain domain of a first and second antibody, wherein the first and second antibody bind to different antigens.

The de Kruif et al reference is directed to forming bivalent or bispecific scFvs but does not discuss at all the light chain sequences or that a common light chain should be selected over other light chains in a bispecific antibody. In fact, the bispecific antibody made in de Kruif did not have the same light chain. Merchant et al is not properly considered prior art and is cited by the Examiner for citing to Nissim et al. Nissim et al. is directed to forming a scFv library to identify antibodies binding to a single antigen and does not discuss bispecific antibodies. Nissim et al. does not disclose the sequence of the variable light chain nor does it suggest that the same light chain variable domain should be used in a bispecific antibody. As discussed above, Hu et al does not disclose either bispecific antibodies or that such antibodies should have the same light chain. Finally, Ridgway et al. does not disclose that bispecific antibodies can or should have the same light chain.

In addition, Applicants also submit that none of the references disclose or suggest a bispecific antibody having a common light chain. Combining the references cannot yield Applicants' claimed invention. In addition, there is no motivation for one of ordinary skill in the art to combine the references because the combination does not yield all of the features of Applicants' invention – the combination does not yield a bispecific antibody having a common

light chain. Applicants respectfully submit that the Examiner is using hindsight reconstruction, which is improper.

Based on the foregoing, applicants respectfully submit that the examiner has not established a prima facie case of obviousness of the claims and request withdrawal of the rejection.

SUMMARY

Applicants submit that all pending claims are in condition for allowance, and notification to that effect is earnestly solicited. The Examiner is invited to contact Applicants' representative if prosecution may be assisted thereby.

Respectfully submitted,

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